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Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority Pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five jears. These addenda represent an updated literature search current as of 1988, plus additional information form Agency files and Program Offices. This addendum is to update the existing Ambient Water Quality Criteria Document for Hexachlorobutadiene.

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Prepared for

OFFICE OF WATER REGULATIONS
AND STANDARDS

Prepared by

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Cincinnati, OH 45268

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PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under contract no. 68-C8-0004.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
bw	Body weight
CRAVE	Carcinogen Risk Assessment Verification Endeavor
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
TLV	Threshold limit value
TWA	Time-weighted average

INTRODUCTION

Under Section 304(a)(1) of the Clean Water Act of 1977 as amended in 1987, the U.S. EPA is required to publish criteria for water quality accurately reflecting the latest scientific knowledge regarding the effects on health and welfare that may occur from the presence of pollutants in any body of water, including groundwater. In accordance with the 1977 act, Ambient Water Quality Criteria Documents (AWQCDs) were developed in 1980 for 65 toxic pollutants or classes of pollutants listed under Section 307(a)(1).

These addenda are intended to serve as an update of the original AWQCDs. The addenda provide the Agency with the latest scientific assessments of potential health hazards associated with these pollutants and serve as guidelines for modifying the current (1980) AWQCDs.

The human health criteria in these addenda are based on Agency verified risk assessment values when available. These values consist of reference doses (RfD) for those chemicals believed to be systemic toxicants (i.e., do not induce cancer) and cancer risk factors for those thought likely to cause cancer in humans. The verification process consists of a review and consensus of risk assessment values provided by an Agency workgroup consisting of scientists from each of the major Agency offices. Assessments for noncarcinogens are verified by the RfD workgroup and those for carcinogens are verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) workgroup. If such values are not available, the criteria are based on the most recent Agency health assessment. In the absence of any appropriate Agency value, RfD values or cancer risk factors are derived by current Agency methods if adequate new data are available, and criteria are recommended based on the proposed RfD or risk factor.

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$RfD = \frac{\text{NOAEL or LOAEL}}{UF(s) \times UF}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RfDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen; Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); Group D - Not Classifiable as to

Human Carcinogenicity (inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multi-stage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQCD on hexachlorobutadiene, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1986 to 1988). New key studies have been evaluated.

REVIEW OF NEW DATA

Toxicologic/Carcinogenic Effects

Ambient water quality criteria for hexachlorobutadiene are based on dose-response data for renal neoplasms in rats (Kociba et al., 1977). The U.S. EPA Agency-wide CRAVE committee verified a classification of U.S. EPA Group C - possible human carcinogen - for hexachlorobutadiene, based upon this study (U.S. EPA, 1986). IARC (1979) determined that there was limited evidence that hexachlorobutadiene is carcinogenic in rats [based primarily upon the Kociba et al., (1977) study]. No human exposure studies regarding hexachlorobutadiene have been located in the available literature, in a recent review by Yang (1988) or in Agency assessments (U.S. EPA, 1984, 1986, 1988a).

Two additional animal studies provide evidence that supports the existing RfD and q_1^* derivations. In one study not reviewed in U.S. EPA (1980), Harleman and Seinen (1979) exposed weanling Wistar rats (10 males and 10 females per group) to hexachlorobutadiene at doses of 0, 0.4, 1, 2.5, 6.3 and 15.6 mg/kg/day by gavage for 13 weeks. Body weight, food consumption, hematologic and clinical chemistry and urinalysis indices were monitored regularly. At the end of the 13-week period, animals were sacrificed and gross and microscopic examinations were performed. In females, significantly decreased urine concentrating ability and degeneration of proximal renal tubules occurred at a dose of 2.5 mg/kg/day. Kidneys of the males were less sensitive than those of the females; however, males showed relatively greater sensitivity than females to liver effects (males had increases in liver weight and cytoplasmic basophilia at $\geq$6.3 mg/kg/day, females had increases in liver weight at $\geq$15.6 mg/kg/day). A NOAEL of 1 mg/kg/day and a LOAEL of 2.5 mg/kg/day were identified.

In a reproductive study performed by Harleman and Seinen (1979), groups of six female Wistar rats were fed diets containing 0, 150 or 1500 ppm of hexachlorobutadiene 4 weeks prior to mating and throughout gestation and lactation, with pups receiving the same dietary levels after weaning. At week 18 of treatment, the animals were killed and necropsied; tissues and organs were examined histopathologically. Extensive renal tubular degeneration, ataxia associated with demyelination and degeneration of femoral nerve fibers, and failure to conceive were observed in the dams at the high-dose level (1500 ppm). Decreased birth weights of the pups and retarded subsequent growth, but no grossly observable malformations, were seen at 150 ppm. At week 18, decreased body weights, increased relative kidney weights, and renal tubular hypercellularity, focal degeneration and necrosis were observed at the 150 ppm level. Assuming that weanling rats consume food equivalent to 10% of their body weight/day, the 150 ppm level corresponds to a LOAEL of 15 mg/kg/day.

The abstract of by Chudin et al. (1985) noted that oral administration of hexachlorobutadiene at doses of 0.6, 5.8 or 37 mg/kg/day to rats for 1 year did not result in pronounced carcinogenic effects, although some benign tumors were seen in the kidney and liver. Additional pertinent details were not provided.

Bioconcentration Factor (BCF)

Pertinent new information concerning the bioconcentration factor for hexachlorobutadiene is currently undergoing Agency review. A BCF value of 392 based on QSAR data has been recommended for hexachlorobutadiene (Thomas, 1989).

QUANTIFICATION OF EFFECTS

The U.S.EPA (1980) derived ambient water quality criteria for hexachlorobutadiene of 4.47, 0.45 and 0.045 µg/ℓ, corresponding to lifetime increased cancer risk levels of 10^{-5}, 10^{-6} and 10^{-7}, respectively. The values assume a 70 kg body weight and a daily intake of 2 ℓ of water and 6.5 g of fish and shellfish with a BCF of 392. Values were calculated from a slope factor of 7.752×10^{-2}/mg/kg bw/day, based upon the Kociba et al. (1977) study, in which groups of ~40 Sprague-Dawley rats/sex/group were fed diets providing 0.2, 2 or 20 mg/kg bw/day of hexachlorobutadiene for 22 (males) or 24 (females) months. The control group was composed of 90 males and 90 females. Statistically significantly ($p<0.05$) increased incidences of renal tubular adenomas and carcinomas were noted in both males and females at the highest dose. A q_1^* was based on the dose-response data for the males (controls, 1/90; low-dose, 0/40; mid-dose, 0/40; high-dose, 9/39).

The slope factor (q_1^*) derived in U.S. EPA (1980) has been verified and rounded to 7.8×10^{-2}/mg/kg bw/day (U.S. EPA, 1986). The Kociba et al. (1977) data remains the best available for use in extrapolating to human exposure risks, using the "unrounded" value of the slope factor (q_1^*) and the same exposure assumptions (2 ℓ/day and 6.5 g seafood) and BCF of 392, the criteria in ambient water for hexachlorobutadiene are as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (µg/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water and consumption of 6.5 g of fish and shellfish	0	0.02	0.20	2.0	20
Consumption of fish and shellfish only	0	0.035	0.35	3.5	35

EXISTING STANDARDS AND CRITERIA

ACGIH (1987) has recommended a TLV of 0.02 ppm (0.24 mg/m^3).

The U.S.EPA (1988a) has verified an oral RfD of $2x10^{-3}$ mg/kg/day for hexachlorobutadiene, based upon a NOAEL of 0.2 mg/kg/day determined from a study by Kociba et al. (1977).

The verified slope factor for oral exposure to hexachlorobutadiene is $7.8x10^{-2}$/mg/kg/day, and the drinking water unit risk factor is $2.2x10^{-6}$ µg/l (U.S. EPA, 1986).

The verified slope factor for inhalation exposure to hexachlorobutadiene is $7.8x10^{-2}$/mg/kg/day, based on the oral data and slope factor. The corresponding inhalation unit risk is $2.2x10^{-5}$ µg/m^3 (U.S.EPA, 1986).

The proposed reportable quantity (RQ) for release into the environment is 1 pound and is based on aquatic toxicity (U.S. EPA, 1988b).

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